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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Chiao, Judy H. et al.	CONFIRMATION NUMBER :	9975
SERIAL NUMBER :	10/616,649	EXAMINER :	Anderson, James
FILING DATE :	July 9, 2003	ART UNIT :	1614
FOR :	**Methods of Treating Cancer with HDAC Inhibitors**		

MAIL STOP AMENDMENT
Commissioner for Patents
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DECLARATION OF MADELEINE DUVIC UNDER 37 C.F.R. §1.132

I, MADELEINE DUVIC, of the University of Texas MD Anderson Cancer Center, Box 434, 1515 Holcombe Blvd., Houston, Texas 77030, declare and state that:

1. I received an M.D. degree from Duke University Medical School in 1977.

2. I am presently employed by Department of Dermatology as Professor and Deputy Chairman at the MD Anderson Cancer Center, Houston, TX. I have been employed by the MD Anderson Cancer Center for 22 years. During my career, I have tested and developed novel methods of treating cancer with various anti-cancer drugs including, SAHA. I was the principal investigator in charge of the Phase II clinical trials of oral SAHA in treatment of cutaneous T-cell lymphoma (CTCL) patients not responsive to conventional treatment. This trial was sponsored by Aton Pharma, Inc., which was a subsidiary of Merck & Co., Inc. I have numerous publications in the field of anti-cancer drug therapy.

3. I have reviewed the Office Action dated September 20, 2007, issued in the above-referenced case. I understand that claims 1, 12-19, 34, 40-47, and 271-276 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Breslow et al. (U.S. Patent No. 6,087,367; hereinafter "Breslow") in view of Curley et al. (Proceedings of

ASCO, 2002, vol. 21, page 6b, entry 1831; "Curley") and Piekarz et al. (Blood, 2001, vol. 98, pages 2865-2868; "Piekarz").

4. I make this declaration to rebut the Examiner's assertion, with which I do not agree. It is my opinion that the currently claimed methods of treating CTCL with SAHA are not obvious in view of the combination of Breslow, Curley and Piekarz. The Examiner asserts that it would have been obvious to treat cutaneous T-cell lymphoma (CTCL) by orally administering SAHA at the claimed doses and administration regimens. I disagree for the reasons set out below.

5. The claims, as amended, specify doses and dosage regimens for the treatment of CTCL. Claim 1 (and the claims that depend therefrom) recite treatment of CTCL with SAHA at a specific dose of 400 mg once daily administered continuously. Claim 34 (and the claims that depend therefrom) recite treatment of CTCL with SAHA at a specific dose of 300 mg twice daily administered 14 out of 21 days.

6. The Examiner concedes that the primary reference, Breslow, does not disclose either (a) the instantly claimed oral dosage regimens of SAHA or (b) the specific treatment of cutaneous T-cell lymphoma with SAHA. Breslow is fatally deficient.

7. Curley does not remedy the deficiencies of Breslow. Curley is an Abstract that refers to a clinical study that was designed to determine the maximum tolerated dose of oral SAHA. The study tested orally administered doses of SAHA from 200 mg daily, 400 mg daily, 400 mg twice a day, 800 mg twice a day, 1600 mg twice a day, and 2000 mg twice a day. Curley does not refer to treatment of CTCL with SAHA at all. Nor does Curley direct the ordinarily skilled artisan to choose the claimed dosage ranges of 400 mg once daily administered continuously (as recited in claim 1 and the claims that depend therefrom) or 300 mg twice daily administered 14 out of 21 days (as recited in claim 34 and the claims that depend therefrom). These specific treatment regimens are unexpectedly superior in the treatment of CTCL, as I have reported in a peer-reviewed publication (on which I am first author) that reports the results of a Phase II clinical trial of oral SAHA for the treatment of CTCL (Duvic et al., (2007) Blood 109(1): 31-39; "Exhibit 1"), which I discuss below.

8. The Office Action contends that treatment of CTCL specifically is taught by Piekarz. However, Piekarz does not refer to use of SAHA in the treatment of CTCL -- rather Piekarz refers to an entirely different molecule -- depsipeptide -- that is structurally unrelated to SAHA. In my view, the suggestion in Piekarz that depsipeptide may be useful in the treatment of CTCL has no bearing on whether a completely unrelated molecule SAHA, is useful in treatment of CTCL (as claimed). Piekarz is silent regarding oral administration of SAHA at the instantly claimed doses and dosing schedules and thus fails to cure the defects of Breslow and Curley. Piekarz relates to a phase I study of intravenously administered depsipeptide in patients suffering from peripheral and cutaneous T-cell lymphoma. Depsipeptide is a compound structurally very distinct from SAHA -- depsipeptide is a cyclic peptide molecule, while SAHA is a hydroxamic acid compound. Furthermore, the two drugs do not share the same mechanism of action. Finally, Piekarz administers depsipeptide intravenously. This is a distinct disadvantage in CTCL patients (as discussed below). According to the claimed invention, SAHA elicits desirable anti-cancer effects in CTCL patients *via* oral administration.

9. SAHA has been approved for such use by the FDA and is currently marketed as Zolinza for that use. A copy of the label as approved has been previously submitted to the USPTO. I note that depsipeptide is not approved by the FDA for use in the treatment of CTCL. Further, the claimed invention provides secondary considerations, such as unexpected results and long felt need and success, that are not taught or suggested by the combination of Breslow, Curley and Piekarz.

10. The study in Duvic compared orally administered SAHA in refractory patients suffering from CTCL (patients with CTCL that were refractory to other treatments). In this study, three separate dosing schedules were used -- (1) once daily continuous administration of 400 mg SAHA, (2) twice daily administration of 300 mg of SAHA for 3 days followed by 4 days rest and (3) twice daily administration of 300 mg of SAHA for 14 out of 21 days. Of these, dosage regimens (1) and (3) -- namely once daily continuous administration of 400 mg of SAHA and twice daily administration

of 300 mg of SAHA for 14 out of 21 days were the most effective in treating CTCL. Notably, Duvic states (page 37, left column, second paragraph) that "[b]ecause the half-life of vorinostat is short (≤ 2 hours), the discontinous dosing schedule of 3 days on and 4 days off used in group 2 may have tipped the balance toward progression compared with continuous therapy regimens of 400 mg daily (group 1) or high dose (300 mg daily for 2 weeks) followed by continuous therapy at 200 mg twice daily (group 3)". This indicates the surprising and unexpected result that continuous administration of 400 mg, or 300 mg daily for 14 out of 21 days produced an advantageous anti-cancer effect in CTCL patients. It was impossible to predict such favorable results from the instantly claimed dosages and dosing schedules from the prior art or the knowledge generally available to those skilled in the art, and that the surprising and unexpected results could only have been obtained by empirically performing the study in patients.

11. The present invention also satisfies a long-felt need in the art for an oral HDAC inhibitor -- SAHA as claimed here -- that can be administered at safe yet effective doses and dosing schedules to treat CTCL. Patients suffering from CTCL exhibit severe skin lesions and are particularly prone to serious skin infections and/or sepsis if subjected to intravenous administration. Any dosage form that would require puncturing or piercing the skin would not be beneficial to the patient and may be detrimental in the context of exacerbating skin infection leading to sepsis. Compared to intravenous depsipeptide (as disclosed in Piekarz), an oral dosage form of an HDAC inhibitor to treat CTCL, and specifically SAHA as claimed here, met a long felt need in the art.

12. For the foregoing reasons, I disagree with the Examiner's assertion that the the claimed invention of treating cutaneous T-cell lymphoma (CTCL) by administration of a once-daily continuous dose of about 400 mg of SAHA, or a twice-daily dose of about 300 mg of SAHA administered for 14 out of 21 days is obvious over Breslow, Curley, and Piekarz.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further

that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Madeleine Duvic

Madeleine Duvic, M.D.

Signed this day 21 of December, 2007

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